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~~69~~. The mucopolysaccharide which comprises glucosamine units, has improved antithrombic activity (as shown by inhibition of coagulation factor Xa) which has a ratio of Yin-Wessler and USP titer of at least 6, and which is shown by the NMR spectra of one of those shown in Figs. 11, 12, 14 or 15. ---

REMARKS

Favorable reconsideration of this patent application is respectfully requested.

Applicants herein petition under the provisions of 37 CFR 1.17 for the necessary three extensions of time to May 22, 1983. A check for the necessary fee is attached herewith. The patent Office furthermore is authorized to debit (or credit if so appropriate) the account of the undersigned # 23-0813 for any discrepancy in the fee, including for the newly added claims, for which a check is also attached.

The attention of the Examiner is respectfully invited to the fact that all claims have been cancelled and replaced by a new set of claims 29 and seq. to facilitate examination of this patent application.

In compliance with 37 CFR 1.75(c) multiple dependency has been obviated, and all claims are now free of multiple dependency. It is therefore respectfully requested that all claims now be treated on their merits.

Applicants respectfully ask that the Examiner's requirement review this specification to correct all typographical errors and omissions, as stated on page 2, paragraph 1 of the Office Action, be held in abeyance until allowable subject matter is indicated in this patent application. If the Examiner does not agree with this suggestion it is respectfully requested that she call the undersigned to so indicate, or so state in the next Office Action.

For the record and because these facts and dates are relevant to the 35 USC 103 rejections, it will be noted that the instant application serial no. 204,505 filed November 6, 1980 is a continuation application of application serial no. 091,164, filed November 5, 1979. Thus, this application benefits already of that date of November 5, 1979. Moreover, that application in turn is based on French patent applications, serial no. 78-31357, filed in France on November 6, 1978 and French patent application, serial no. 79-18873, filed July 20, 1979, all of which applications are referred to in the instant declaration.

A certified copy of these two French applications are of record to support the claims of priority under 35 USC 119,

With respect to the rejection of the claims under 35 USC 112, second paragraph, which was applied to the previous three claims, it is respectfully submitted that the instant claims overcome said rejection. Some of the claims herein presented do still maintain the term "fraction" to which the Patent Office objected pre viously as being superfluous. However, it will be noted by review of the patent application that the term "fraction" helps to define the subject matter claimed in that this term further distinguishes the mucopolysaccharide claimed

from heparin. Designating the subject matter claimed as a "mucopolysaccharide fraction" rather than a "mucopolysaccharide" therefore contributes to definiteness under 35 USC 112, paragraph 2. It is submitted that the claims do distinctly point out and claim with the requisite particularity the sub ject matter which applicants consider their invention.

It will be recalled that the instant application deals with specific mucopolysaccharides which have particularly high antithrombic activity. The anti-clotting properties of heparin are well known. However, as has been taught in the specification, the overall or general anti-clotting properties of heparin are not always desirable. The overall anti-clotting activity of heparin (which is measured in USP units) can be responsible for serious hemorrhaging. Thus heparin is known to have a very narrow therapeutic index, i.e. bleeding can occur at a dosage of heparin which is marginally greater than that called for to prevent extension of thrombi.

Various approaches to avoid the risks of hemmorhaging have been undertaken by various reserach groups. It has not been able to predict what depolymerized heparins or other parameters are responsible for the sought-for antithrombic property. See for instance for a further discussion of these problems confronting one skilled in the art, U.S. patents 4,303,651 to Lindhal et al., December 1, 1981 (Kabi AB); Lindhal et al., Proc.Natl.Acad.Sci. USA, 76, No. 7, pp 3198-3202, July 1979 (made of record here as Exhibit I); 4,281,108 to Fussi, July 28, 1981, (Hepar Indistries, Inc.). Applicants have now successfully synthesized particular mucopolysaccharides which do not possess the high general anti-clotting property of heparin. In contrast,

the mucopolysaccharide fractions of the invention sharply distinguishes over heparin in possessing remarkably high and specific antithrombotic activity (which is measured in Yin-Wessler units).

The claims are drawn to specific mucopolysaccharides which have a highly selective antithrombic activity, namely the property of inhibiting the factor Xa. See for instance page 6 of the specification. This specific activity is reflected in certain claims, for instance, method of use, claim 68. The position in the coagulation cascade of coagulation factor X and the therapeutic effect of its inhibition is described in the specification. The mucopolysaccharides of the invention are further identified by a particularly characteristic, namely that the ratio of the Yin-Wessler titer (a measurement of the anti-Xa effectiveness) to the USP titer is remarkably high. The mucopolysaccharide fractions claimed are also identified by additional structural characteristics (as evidenced by the characteristic NMR spectrum) as is called for instance in claims 41, 42-45, 47, 49, 54 and 56.

The claims are also drawn to a specific process for obtaining the mucopolysaccharide fractions, see for instance, claim 59. It will be noted that these claims call for a specific series of steps which comprise suspending in a particular medium a heparin of a stated molecular weight range and then separating the insoluble fraction followed by additional series of steps.

Other claims are drawn to the valuable therapeutic compositions such as claims 60-62.

Claim 63 is drawn to the treatment of thrombosis.

Attention of the Examiner is respectfully invited to claims 64-68 which are based on the specification pages 34-36, and to claim 69 based on Figs 11, 12, 14 and 15. Claiming by reference to Figs. which represent NMR spectra (and have been called by the courts to be as precise and exact as "finger-prints"), is proper.

The rejection of the product, composition and method of use claims on the cited art is, it is urged, respectfully, not proper. The effective dates of Fussi (document No. C), Lindhal et al (document No. D), Takacs et al (document No. E) are all posterior to applicants'. The publication of Lindhal et al does not disclose or suggest that subject matter claimed herein. It does not have the characteristic features of that called for by the claims.

Moreover, none of the specific steps of the process claims (nor of course of its products) are suggested or disclosed by the other cited references, Choay et al and Schmer.

Schmer disclosed affinity chromatography which involves various steps including the dissolution of commercial heparin in a specific solvent, passsing the solution on an affinity column, elution and recovery of certain fractions. The process is based on recovery of fractions which have differential affinity. The process has no relevance with respect to the process claimed.

Neither is the process nor the products of Choay et al suggestive or teaching the process or products claimed. In that patent, there is disclosed a method for obtaining a salt of heparin having a particular metallic cation different from sodium, or a mixed salt of heparin with reduced sodium salt content. None of the process described therein is relevant to the process claimed.

The products which are obtained are akin to the traditional heparin except that they are a different salt than the sodium heparinate, as is traditional.

In view of the above remarks, it is evident that the subject matter claimed including the method of administration and the biological compositions, are not suggested or taught by either one of the references considered individually or together in any combination with the primary references.

In conclusion, applicants note that the claims as presented in this application and those in copending application serial No. 301,611 are not claiming the same subject matter.

In the event that the Examiner considers that the prosecution of this patent application may be favorably advanced by a discussion with the undersigned and any outstanding issues narrowed, she is respectfully invited to call the undersigned at the telephone number indicated below.

Respectfully submitted,

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Attachments: Exhibit I, Structure of Antithrombin-binding Site in Heparin, Lindhal et al, Proc.Natl.Acad.Sci.USA., Vol. 76, No. 7, pps.3198-3202, July, 1979.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on

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5/25/83
Date